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Docking Study of Naphthalene Compounds from *Eleutherine Bulbosa* as Antidiabetic Agents on Multiple Receptors

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ABSTRACT. Diabetes Mellitus is a severe disease to the world health community; it is estimated that 700 million people worldwide will suffer from it. The approach taken to this disease includes improving lifestyle and pharmacological therapy. Recent pharmacological therapeutic approaches include inhibiting the α-glucosidase enzyme, the dipeptidyl peptidase 4 (DPP-4) enzyme, and the sodium-glucose co-transporter-2 (SGLT-2) protein. This research aims to conduct a docking study on three naphthalene compounds from *Eleutherine bulbosa* against three receptors: α-glucosidase, the DPP-4, and the SGLT-2 protein. The methods used are protein structure preparation, docking protocol validation, preparation of *E. bulbosa* test ligand structures, and molecule docking for test compounds. Validation was carried out by calculating the Root Mean Square Deviation (RMSD) values using PyMOL software; the results showed that the RMSD value of native ligands was <2Å. Molecular docking of the test compounds was conducted using Autodock Vina 1.2.3 ver 2020. Eleutherinoside A showed the highest binding against the α-glucosidase and DPP-4 protein. Eleuthoside B has the most increased binding to SGLT-2 protein. The research concluded that three naphthalene compounds from *E. bulbosa* can be used as an antidiabetic agent.

Keywords: Antidiabetic; Docking study; *Eleutherine bulbosa*; Naphthalene; α-glucosidase; DPP-4; SGLT-2

INTRODUCTION

Diabetes mellitus is a metabolic disorder in which the patient has high fluctuations in blood glucose levels. This can be due to insufficient insulin production and the insensitivity of insulin receptors (Ushasri & Anusha, 2015). With 463 million cases worldwide and predicted to reach 700 million by 2045, diabetes has emerged as a severe health concern (IDF, 2019). About 90% of instances of diabetes are type-2 diabetes (T2D), which is most prevalent and is brought on by a decreased sensitivity to insulin in the muscle and liver cells (ADA, 2013a; IDF, 2019). T2D can lead to several serious complications, including cardiovascular disease, retinopathy, nephropathy, kidney failure, and amputation of lower extremities (ADA, 2013b); this serious threat underlines the need for selective and effective therapeutic approaches.

Type 2 diabetes is treated primarily with diet and exercise, then with oral anti-diabetic medications and occasionally subcutaneous insulin injections (El-Kaissi & Sherbeeni, 2011). According to the findings of multiple multicenter trials, the medications listed above may lower blood sugar levels and reduce the chance of complications from diabetes. Presently, existing anti-diabetic drugs do, however, have certain drawbacks. For instance, gastrointestinal adverse effects are commonly linked to metformin use (Nissen & Wolski, 2007). Thiazolidinediones may elevate cardiovascular disease risk. These adverse effects prevent it from being widely used in clinical settings.

One approach to managing T2D is inhibiting the α-glucosidase enzyme found in the brush border of the small intestine, where the pH value varies from 6.0 to 7.4 throughout the intestine (Fallingborg, 1999). Here, the enzyme hydrolyzes carbohydrates to glucose, which is transferred to the bloodstream. Thus, α-glucosidase inhibitors can reduce postprandial blood glucose levels by inhibiting the conversion of dietary carbohydrates into glucose in the small intestine. The inhibition of α-glucosidase is a well-established approach to managing T2D (Derosa & Maffioli, 2012).

A different strategy for managing type 2 diabetes is to inhibit the dipeptidyl peptidase 4 (DPP-4) enzyme. This enzyme primarily acts on the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), responsible for maintaining glucose homeostasis by secreting more insulin and less glucagon (Capuano et al., 2013). Enteroendocrine L cells in the small intestine secrete

the hormone GLP-1, which lowers blood glucose by inducing insulin production, reducing glucagon concentrations, and delaying gastric emptying (Pathak & Bridgeman, 2010). The hormone GIP is released by the stomach and the proximal small intestine neuroendocrine K-cells (Gupta & Kalra, 2011).

We can also employ the strategy of inhibiting the proteins that make up the sodium-glucose co-transporter-2 (SGLT-2). Reabsorbing filtered glucose from the tubular lumen is how the kidneys' proximal convoluted tubules, which contain SGLT-2 proteins, carry out their physiological role. There are now four SGLT-2 inhibitors that have received FDA approval: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Nespoux & Vallon, 2020). Each of the four SGLT-2 inhibitors lowers the renal threshold for glucose (RTG), increases urine glucose excretion, and decreases the reabsorption of filtered glucose. Inhibitors of SGLT2 reduce HbA1c by 0.7% (Plosker, 2014).

The presence of therapeutically important phytochemicals in medicinal plants makes them very promising for treating a wide range of diseases (Bindu & Narendhirakannan, 2019). Traditional plants are thought to have significant antidiabetic properties without causing adverse side effects; they are rich in compounds such as flavonoids, alkaloids, phenolic compounds, and tannins that help increase the efficiency of pancreatic tissue by reducing intestinal glucose absorption or increasing insulin secretion (Arifah et al., 2022). Indonesia has a rich biodiversity, and ethnic groups use traditional medicines as anti-diabetic drugs. A total of 229 species of medicinal plants in Indonesia from 70 families used to treat diabetes mellitus were recorded by Arifah and her colleague. Asteraceae and *Orthosiphon aristatus* (Blume) Miq are the two most prevalent plant families and species (Arifah et al., 2022). The Eleutherine genus from the Iridaceae family is a plant genus with various biological activities, including antidiabetic (Kamarudin et al., 2021).

For the Dayak people on the island of Kalimantan, Indonesia, *Eleutherine bulbosa* is a familiar plant, similar to *Eleutherine americana* (Iridaceae) or Dayak garlic (local name). South America is home to the eleutherine plant. *E. americana*, *E. plicata*, and *E. latifolia* are a few more species in this genus. Africa, Malaysia, Indonesia (Kalimantan and West Java), and the Philippines (Luzon, Leyte, Negros, Mindanao) are some of the places where this plant grows and spreads naturally. The Dayak tribe uses the plant, which is highly adaptable to grow in a variety of climates and soil types, to treat ailments such as cancer, high blood pressure, diabetes mellitus, cholesterol, and ulcers. The most common traditional preparation involves boiling seven cloves of *E. bulbosa* bulb in three glasses of water until reduced by half and then taking the water one to three times a day (Arung et al., 2009; Kuntorini et al., 2010).

The bioactivities of *E. bulbosa* and its chemical constituents have been the subject of very few studies. Shibuya et al. (1997) reported the presence of eleuthoside A, B, and C from the water-soluble fraction of *E. bulbosa* methanolic extract, as well as eleutherol, eleutherin, and isoeleutherin from the ethyl acetate soluble fraction of *E. bulbosa* methanolic extract (Shibuya et al., 1997). Ieyama et al. (2011) reported the alpha-glucosidase inhibitory activity of three naphthalene derivatives in the methanolic extract of *Eleutherine americana* (Ieyama et al., 2011).

In our effort to develop a standardized herbal-based medicine from Indonesian medicinal plants, bawang dayak, a docking study of three naphthalene compounds of *E. bulbosa* was performed to ensure which compounds are responsible for the antidiabetic agents in three different receptors.

EXPERIMENTAL SECTION

Instrumentation

Computational study in this research was performed on Personal Computer Dell WorkStation, Linux Ubuntu 20.04.3 LTS OS, Intel® Xeon(R) W-2223 CPU @ 3.60GHz octa-core; RAM 16 GB and GPU NVIDIA RTX 4060 TI.

Protein Structure Preparation

The protein structures for α-glucosidase (PDB ID: 3w37) (Mattei, 2010), DPP-IV (PDB ID: 3kwf) (Tagami, 2013), and SGLT-2 (PDB ID: 7VSI) (Niu, 2022) were downloaded from the www.rcsb.org website. Subsequently, we utilized BIOVIA Discovery Studio 2020 software to separate solvent residues (water), native ligands, and other non-standard residues from the proteins. Further, we optimized the proteins by adding Kollman charges, while the native ligands were assigned Gasteiger charges using the AutoDock program.

Docking Protocol Validation

The prepared native ligands were subjected to redocking based on their original coordinates using Autodock Vina 1.2.3 ver. 2020. The positions and orientations of standard ligands interacting with amino acids were visualized using BIOVIA Discovery Studio version 2017. Validation was carried out by calculating the Root Mean Square Deviation (RMSD) values using PyMOL software ver 2.5. If the RMSD value for the native ligands was <2Å, the docking protocol was acceptable and valid for further use in docking studies with test compounds (Hevener, 2009; Zubair et al., 2016).

Preparation of *E. bulbosa* Test Ligand Structures

(Bianchi & Ceriotti, 1975) (Paramapojn et al., 2008) (Hara et al., 1997; Zhengxiong et al., 1986) (Alves et al., 2003) (Chen et al., 2018) (Chen et al., 2018) (Hara et al., 1997; Zhengxiong et al., 1986) (Chen et al., 2008) (Chen et al., 2018) (Chen et al., 2018). The 2D molecular structure of *E. Bulbosa* metabolite compounds was generated using

ChemDraw. Subsequently, these structures were optimized using Chem3D software employing the MMFF94 force field.

Molecule Docking for Test Compounds

Molecular docking of the test compounds was conducted using Autodock Vina 1.2.3 ver 2020, following the validated docking protocol. For alpha-glucosidase, the coordinates were set as x=0.699, y=-1.968, z=-23.212, and a grid box size of 30 x 48 x 30 Å was employed. For DPP-IV, the coordinates used were x=46.499, y=51.835, z=34.033, with a grid box size of 30 x 30 x 40 Å, while for SGLT, the coordinates were set as x=39.007, y=51.963, z=45.448, and a grid box size of 30 x 30 x 30 Å.

RESULTS AND DISCUSSION

The research was carried out to determine the potency of naphthalene compounds secondary as an α-glucosidase, DPP-4, and SGLT-2 inhibitor in interactions of native ligands and secondary metabolites of *E. bulbosa* on α-glucosidase, DPP-4, and SGLT-2 macromolecules inhibitors.

The docking results of the native ligand have Root Mean Square Deviation (RMSD) values, including acarbose 0.6481 Å, DPP-4 0.5006 Å, and SGLT-2 RMSD 1.0501 Å, which means the docking result is valid (<2 Å) (Hevener, 2009; Zubair et al., 2016).

Table 1 presents predictions regarding naphthalene compounds derived from *E. bulbosa*, explicitly focusing on their potential as antidiabetic agents targeting multiple receptors. The assessment involves a comparative analysis of binding energy values for these compounds, compared with the native ligands. Binding energy, conventionally expressed as a negative value, holds significance in evaluating the stability profiles of ligand-protein complexes formed during docking simulations. This study primarily aims to comprehend the stability of naphthalene compounds from *E. bulbosa*, as evidenced by their respective binding energies. Negative critical energy values can be interpreted as the energy released during complex formation. Notably, a more negative binding energy signifies a more stable ligand-protein complex, reflecting the exothermic of the complex formation process and a more significant release of energy (Agnieszka, 2011; Ernst et al., 2006; Sim, et al., 2008).

The docking simulation results reveal that Eleutherinoside A exhibits a lower binding energy (-8.322 kcal/mol) than acarbose (-8.311 kcal/mol) as the positive control of the alpha-glucosidase receptor. This outcome suggests that Eleutherinoside A forms a more stable complex with the alpha-glucosidase receptor, indicating its potential inhibitory activity. Furthermore, Eleutherinoside A also demonstrates optimal binding affinity on the DPP-4 receptor, with a binding energy of -9.517 kcal/mol, close to the critical point of Carmegliptin as the native ligand (-9.678 kcal/mol). In the case of the SGLT-2 receptor, Eleuthoside B emerges as a noteworthy compound with the best binding energy value at -11.429 kcal/mol, surpassing Empagliflozin with a binding energy of -10.847 kcal/mol. These results suggest that Eleutherinoside A holds promising inhibitory activity on the alpha-glucosidase and DPP-4 receptors, while Eleuthoside B strongly interacts with the SGLT-2 receptor. This result highlights the potential of these naphthalene compounds derived from *E. bulbosa* as antidiabetic.

Enzyme of the exo-type, α-glucosidase, is essential for catalyzing the hydrolysis of α-glucosidic bonds at the non-reducing ends of substrate molecules. Interestingly, the majority of α-glucosidases favor trisaccharides and disaccharides as substrate (Ernst et al., 2006; Sim et al., 2008). The structural configuration of α-glucosidase encompasses a catalytic domain with a (β/α)8-barrel fold, along with N- and C-terminal environments characterized by β-sandwich structures (Ernst et al., 2006; Sim et al., 2008). The catalytic domain has brief insertions known as subdomains b1 and b2, found in the loops following the third and fourth β-strands, respectively. The N-loop's Phe236 and Asn237 are essential for the long-chain substrates' selectivity. Ser497 is ready to bind the substrate at subsite +4 in subdomain b2, but the first two catalytic aspartic acid residues, Asp-469 and Asp-568, are critical for substrate binding at subsites +2 and +3 (Tagami et al., 2013; Tagami et al., 2013).

To understand their molecular mechanism activity, we successfully visualize in 2D interactions in which the hydroxyl group of the sugar moiety in Eleutherinoside A is observed to interact with the catalytic site of α-glucosidase, particularly with Ser497, forming hydrogen bonds that play a crucial role in substrate binding. Similar interactions are noted in Eleuthoside B, where interactions with the catalytic site involve the aspartic acid residues Asp469 and Asp568, forming hydrogen bonds. Additionally, hydrophobic interaction (π-π) is observed between the aromatic structure of Eleuthoside B and Phe236, contributing to its specificity for long-chain substrates. These interactions resemble those surveyed in acarbose, the positive control, where interactions occur with essential amino acid residues, particularly Asp568 and Asp469, through hydrogen bonding (**Figure 1**). These findings indicate that Eleutherinoside A and Eleuthoside B can inhibit α-glucosidase based on their interactions with the crucial catalytic site involved in glucose metabolism. The presence of aglycones in both structures contributes to their binding affinity with the catalytic site of α-glucosidase. This result correlates with previous research (Gendokesumo, 2022) that highlighted the significant impact of the aglycone structure of Momordicoside B from *Momordica charantia* Linn. on its affinity for α-glucosidase. On the other hand, it also aligns with a prior study (Jung et al., 2017), which reported that naphthalene

glycosides from *Cassia obtusifolia* demonstrated inhibitory activities against human α-glucosidase. Nevertheless, Eleutherol exhibited the lowest affinity and could not interact with the catalytic site of α-glucosidase. This limitation renders Eleutherol less promising for development as an α-glucosidase inhibitor. Our research corroborates these findings, providing valuable insights into the differential inhibitory potentials of various compounds on α-glucosidase activity.

As the T-cell antigen CD26, dipeptidyl peptidase-4 (DPP-4) is a multifunctional protein with various functions (Deacon, 2019). DPP-4 is a highly conserved type II transmembrane glycoprotein with three distinct domains: an extracellular domain, a transmembrane domain, and a 6-residue N-terminal cytoplasmic tail. (Deacon, 2019). This enzyme, encoded by the DPP4 gene, is ubiquitously expressed on cell surfaces, playing pivotal roles in immune regulation, signal transduction, and apoptosis (Mulvihill & Drucker, 2014).

Through its molecular interactions with ADA, caveolin-1, caspase recruitment domain-containing protein 11, and the T cell antigen CD45, DPP-4 initiates intracellular signaling. In addition, it increases glucose-dependent insulinotropic polypeptide (GLP-1) and active incretin hormone (GLP-1), which are released by enteroendocrine L and K cells, respectively, and act as substrates for DPP-4 (Mulvihill & Drucker, 2014). Recognizing DPP-4 as a potential target for type 2 Diabetes Mellitus underscores its significance (Alsamghan et al., 2020). In molecular docking, DPP-4 inhibitors emerge as valuable tools for elevating insulin levels and prolonging the activity of GLP-1 and GIP, thereby proving effective in glycemic control (Pantaleão et al., 2015).

Two basic approaches are usually used in the design of DPP-4 inhibitor medications: substrate-based structure synthesis and non-substrate-based structure synthesis. Proline mimetics and other compounds created using the substrate-based inhibitors technique interact with the DPP-4 protease's S1 pocket, with the P2-substituent occupying the S2 pocket and the P1-substituent occupying the S1 pocket. Covalent or non-covalent bonds are involved in these interactions (Idris & Donnelly, 2007). Essential amino acid residues with the catalytically active Ser630 generate reversible covalent connections in the DPP-4 structure. Other interactions occur concurrently with a protonated amino group, forming hydrogen bonds with negatively charged surface areas of protein residues Tyr662, Glu206, and Glu205 (Ahrén & Schmitz, 2004; Kumar et al., 2021; Kushwaha et al., 2014).

In **Figure 2**, Eleutherinoside A bonds hydrogen with Ser630 via a carbon-hydrogen interaction, where the O atom in the aglycone acts as a proton acceptor. Hydrogen bonding occurs with Tyr662, while interactions with Glu205 involve van der Waals forces. On the other hand, Eleuthoside B interacts with the essential DPP-4 amino acid Ser630 through hydrogen bonding facilitated by an ether bridge in the aglycone structure. Similar interactions are observed with Tyr662 and Glu205, involving hydrogen bonds with hydroxyl groups in the aglycone, but the interaction with Glu206 occurs via van der Waals forces. Notably, these docking results closely resemble the interactions seen with Carmegliptin, the positive control, where bonding occurs with crucial DPP-4 residues, namely Glu205, Glu206, and Tyr662, through the N group in Carmegliptin. While Carmegliptin exhibits superior binding affinity due to more robust interactions, the interaction of naphthalene from *E. bulbosa* with the DPP-4 active site suggests its potential as a DPP-4 inhibitor. Further development is warranted to enhance its binding affinity with the DPP-4 protein. Our study is the first to report the potential of naphthalene derivatives from *E. bulbosa* as antidiabetics, particularly as DPP-4 inhibitors.

A crucial member of the sodium-glucose cotransporter family, sodium/glucose cotransporter 2 (SGLT2) is a glucose transport protein dependent on sodium and expressed by the human SLC5A2 gene. A protein called SGLT2 is found in the early proximal tubule. It is essential for reabsorbing 80–90% of the glucose filtered by the kidney glomerulus. SGLT1 and other proteins in the more distal portions of the proximal tubule are mainly responsible for the remaining glucose absorption. Surprisingly, SGLT2 inhibitors—also called gliflozins—can lower blood glucose levels and are consequently considered for managing type 2 diabetes (Shubrook, 2015; Wells et al., 1993). Sodium-glucose cotransporter 2 (SGLT2) is an essential protein for transporting glucose in the kidney, responsible for almost 90% of glucose reabsorption from primary urine (Wang et al., 2022).

Structurally, The SGLT2 protein contains conserved residues, namely Phe98, His80, and Glu99, at the SGLT2 substrate binding site, which are instrumental in hydrogen bond formation and hydrophobic interactions. This structural insight enables targeted and selective inhibition (Pang et al., 2023). In the context of this research, Eleuthoside B emerges as the compound with the highest affinity, outperforming other naphthalene compounds from *E. bulbosa*, by interacting specifically with conserved residues, including Phe98 through van der Waals interactions, as well as His80 and Glu99 at the SGLT2 site. Docking results reveal weak interactions, particularly van der Waals forces, occurring at the aromatic ring of Eleuthoside B. The alkyl group attached to the aromatic system interacts with His80 through hydrophobic interactions (π-alkyl), facilitating Eleuthoside B's bound to the SGLT2 receptor. Furthermore, Eleuthoside B exhibits hydrophilic interactions on its polar side, wherein the aglycone binds with amino acids Asn75, Thr87, Asp454, and Gln457 at the SGLT2 receptor, forming hydrogen

bonds. This hydrophilic interaction aids Eleuthoside B's sustained binding to the SGLT2 receptor. Remarkably, these findings parallel those of Empagliflozin, a positive control, which interacts with conserved residues, such as Glu99 through van der Waals forces, but also exhibits hydrophobic interactions with His80 (π-alkyl) and Phe98 (π-π). In contrast, Eleutherinoside A, a naphthalene derivative from *E. bulbosa*, demonstrates fewer molecular interactions, notably missing interactions with conserved residues (**Figure 3**). This leads us to hypothesize that the lower affinity of Eleutherinoside A may be attributed to its diminished binding capacity compared to Eleuthoside B. Notwithstanding, eleutherol interacts with the conserved residues, notably Phe98, His80, and Glu99, through weak van der Waals forces, though not as optimally as Eleutherinoside A in its interaction with the SGLT2 receptor.

Table 1. Docking results of test compounds and native ligand (standard drug) on α-glucosidase, DPP-4, and SGLT-2 protein

No	Ligand	Binding Energy (kcal/mol)		
		α-Glucosidase	DPP-4	SGLT-2 Protein
1	Acarbose (RMSD 0.6481 Å)	-8.311		
2	Carmegliptin (RMSD 0.5006 Å)		-9.678	
3	Empagliflozin (RMSD 1.0501 Å)			-10.847
4	Eleutherol	-6.220	-7.071	-8.720
5	Eleutherinoside A	-8.322	-9.517	-7.728
6	Eleuthoside B	-8.244	-8.832	-11.429

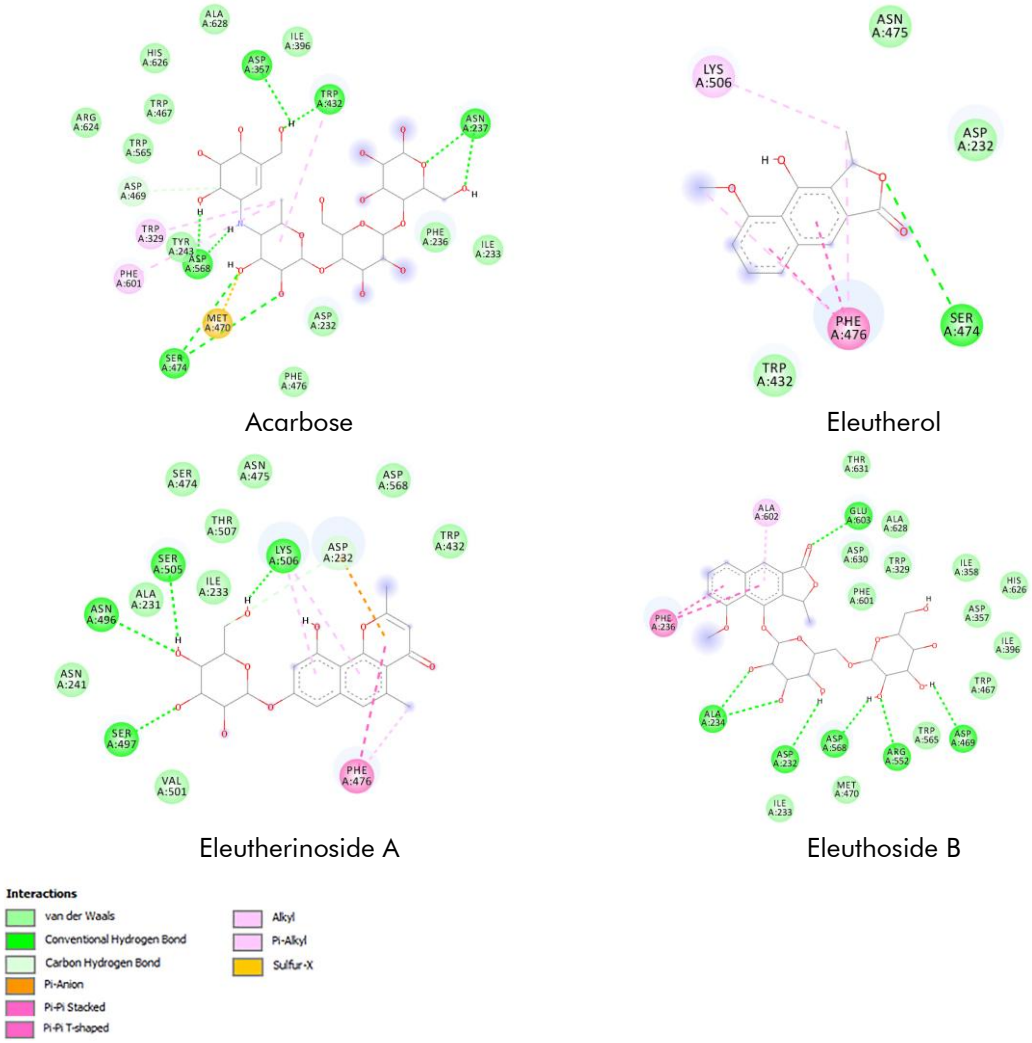

Figure 1. Molecular interactions of acarbose and naphtalane compounds from *E. bulbosa* againts α-glucosidase receptor

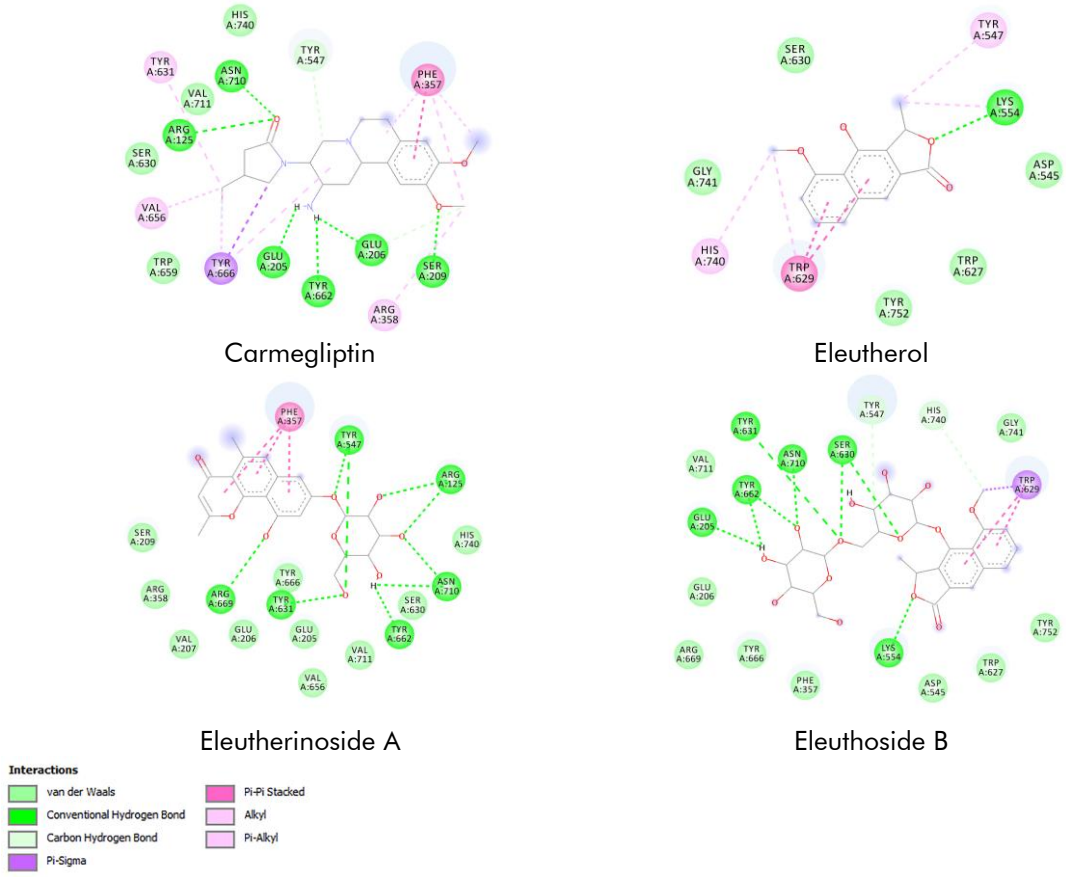

Figure 2. Molecular interactions of carmegliptin and naphtalane compounds from *E. bulbosa* against DPP-4 receptor

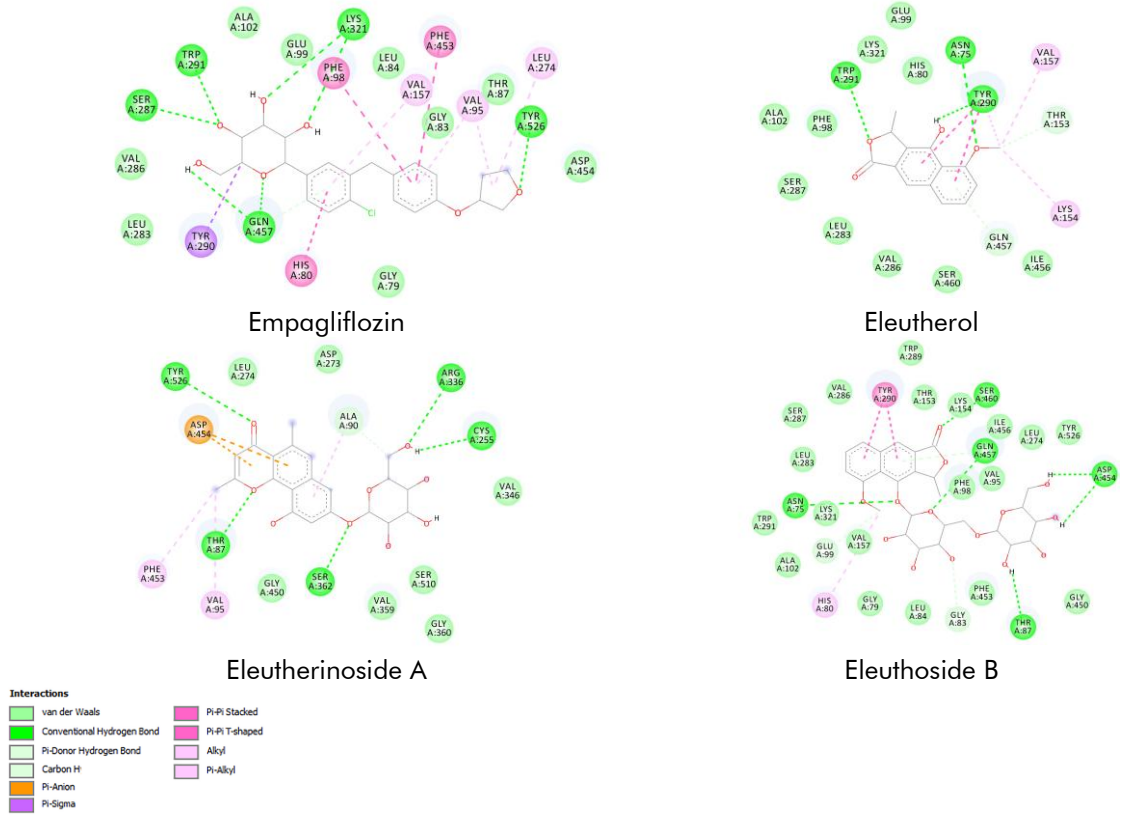

Figure 3. Molecular interactions of empagliflozin and naphtalane compounds from *E. bulbosa* against SGLT-2 receptor

CONCLUSIONS

In conclusion, the naphthalene compounds from *E. bulbosa*, eleutherinoside A, and eleuthoside B showed the potential as antidiabetic agents on α-glucosidase, DPP-4, and SGLT-2.

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